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(54) Abstract Title
Stable apomorphine solution formulations

(57) An injectable aqueous solution comprising apomorphine hydrochloride hemihydrate as an active ingredient in combination with sodium metabisulfite as an antioxidant, methyl parahydroxybenzoate and benzyl alcohol as preservatives and antimicrobials, and sodium edetate as a stabilising and chelating agent. The pH of the solution is preferably 3.7 and the solution is sterilised by filtration under nitrogen pressure.

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STABLE APOMORPHINE SOLUTION FORMULATIONS

The present invention relates to a formulation containing apomorphine hydrochloride hemihydrate in solution. In particular the invention refers to a formulation in aqueous solution stable for at least two years up to 25° C in the presence of excipients and able to warrant low microbial count after opening and during use.

Parkinson's disease is a progressive degenerative disorder of the Central Nervous System characterised by a loss of neurones in a particular region of the brain, the substantia nigra. Said neurones, when present, synthesise and release dopamine, the neurotransmitter which is in chemical communication with other cells, and are thus referred to as dopaminergic neurones. Symptoms of said disease include rigidity, resting tremor (shaking), poverty of movement (akinesia), slowness of movement (bradykinesia) and changes in gait and posture. Its treatment is based on compensating for the lack of dopaminergic neurotransmission caused by the loss of this dopaminergic population of neurones. The classical treatment of choice involves the chronic oral administration of levodopa which is able to cross the blood-brain barrier, unlike dopamine. Levodopa is a prodrug and is decarboxylated in the brain to form dopamine. In order to increase the intracerebral availability of unmodified drug, peripheral decarboxylase inhibitors are usually co-administered.

However, after an initial treatment period of 3-6 years, in which an optimal clinical effect of oral levodopa is observed, movement abnormalities appear in approximately 40-60% of patients. Said abnormalities, likely due to variations in the drug plasmatic levels which reduce the intracerebral availability of the drug, consist of involuntary movements during the periods

of clinical improvements (the so-called "on" phases) and the re-emergence of parkinsonian symptoms at other times (the so-called "off" periods).

Several drugs which act at the postsynaptic dopamine receptor have been recently found to alleviate these abnormalities of chronic levodopa therapy and substantially increase the duration of "on" periods of clinical improvements. The most powerful and effective of these agents, apomorphine, is limited by a short duration of action and side effects. Oral administration route is indeed unsatisfactory due to the breakdown of the drug in the liver, stomatitis and the development of buccal ulcers. Therefore, in order to circumvent said drawbacks, a liquid pharmaceutical form suitable for parenteral (subcutaneous) administration is of great therapeutical advantage.

The availability of ready-to-use vials containing a suitable volume of the formulation to be automatically delivered by a portable infusion mini-pump even in the domiciliary setting would constitute a further advantage.

Said formulation and system for delivery would turn out to be particularly useful for complicated parkinsonians, who, besides the inherent shortcomings of the drug, often show severe movement disorders as well as difficulty in swallowing.

An important requirement for an acceptable formulation is its physico-chemical stability in order to guarantee adequate shelf life.

It is however known from literature that the preparation of therapeutical formulations of apomorphine solutions is problematic due to its chemical instability. Apomorphine is indeed a rather unstable molecule that easily degrades in solution, when exposed to the atmosphere. The oxidation pathways are very dependent on the pH in the solution and they were described first by Rehse K (Arch. Pharm. 302, 487, 1968).

One of the main degradation pathways is the oxidation of the catechol

(dihydroxybenzoic) group, which gives rise to intensely coloured products (chinoids). The white or white-greyish apomorphine crystals quickly turn greenish on exposure to air and light.

The major problem alleged to the preparation of apomorphine injectable formulations is therefore to obtain stable solutions which also remain clear and colourless (or pale yellow). Although the depth of colour is not a reliable indicator of the extent of oxidation and deeply pigmented solution could still contain 98% of the original substance (Burkman AM J Pharm Sci 54, 325-326, 1965), nevertheless if the solution has turned green it is necessary to discard the formulation even though it is not sure it has been gone bad. Stable formulations under environmental storage conditions (room temperature and, at the occurrence, protected form light) are particularly preferred. Antioxidants, such as ascorbic acid, disodium edetate, sodium pyrosulfite or sodium metabisulfite have been used to overcome the above mentioned drawback. However antioxidants can be used only in small concentrations as sodium metabisulfite, for example, gives rise to precipitates due to complexation with apomorphine. The rate of oxidation can be also retarded by adjusting the pH of the solution between 3 and 4 and by eliminating dissolved oxygen.

Other requirements for an acceptable parenteral formulation are sterility as well as adequate microbiological quality during use. Since apomorphine is administered by slow infusion for a period of even 24 hours, preservatives should be added to the solution in order to avoid microbial contamination after opening of the vials.

However the presence of further excipients such as preservatives may affect the stability by quali-quantitatively affecting the degradation pathways; moreover preservatives could introduce contaminants such as trace of heavy

metals which act as catalysts of oxidation reactions.

In consideration of all problems and disadvantages reported, it would be highly advantageous to provide vials containing a suitable volume of a sterile apomorphine hydrochloride formulation to be efficiently delivered by subcutaneous infusion, said formulation further providing adequate shelf-life of the active ingredient at room temperature and warranty of low microbial count after opening and during use.

The stability and the acceptability of the preparations of the prior art are rather unsatisfactory from the chemico-pharmaceutical point of view. Furthermore, upon long-term storage, a decrease of the content is often observed which do not conform with the current ICH (International Conference Harmonisation) requirements for pharmaceutical formulations.

Maloney TJ et al. (Aust J Hosp Pharm 1985, 15, 34) reported apomorphine hydrochloride 0.1% w/v solution containing sodium metabisulfite 0.1% w/v prepared by aseptic filtration. The air was replaced by sterile nitrogen. Nevertheless, the obtained product turned out to be of limited stability (one year) and it had anyway to be stored below 8°C.

Brookes RW et al. (Pharmacy Practice Research 1991, 247, R11) described solutions of apomorphine hydrochloride 1% w/v sterilised by autoclaving containing sodium metabisulfite 0.15% w/v and/or other antioxidants (sodium edetate 0.05% w/v and ascorbic acid 0.1 w/v. All the preparations exhibit some degradation already at the release.

Lundgren P et al. (Acta Pharm Suecica 1970, 7, 133) investigated the stability of apomorphine hydrochloride 0.5% w/v solutions with different combinations of sodium pyrosulfite 0.1% w/v, sodium edetate 0.01% w/v, 0.1 M hydrochloric acid 0.3% w/v. Samples were stored unopened at 25° C and

between 2° and 8° C and at 25° C with frequent opening of the containers. After 205 days, up to 10% degradation has occurred in any preparation.

Wilcox R E et al. (J Pharm Sci 1980, 69, 974-976) demonstrated that ascorbic acid 10% w/v or sodium bisulphite 0.052% w/v and 2% w/v limited degradation to less than 10% when 0.02% w/v apomorphine hydrochloride aqueous solutions were stored at room temperature.

A stable apomorphine hydrochloride 1% w/v solution for injection is yet currently on the market as 2 and 5 ml vials (Britaject®) containing sodium metabisulphite and HCl to adjust the pH.

It has now been found and this the object of the present invention that a formulation of 1% w/v apomorphine hydrochloride in aqueous solution in the presence of a particular quali-quantitative combination of excipients turned out to be sufficiently physical and chemical stable for pharmaceutical use by contemporaneously warranting good microbiological quality after opening and during use as specifically requested by the ICH/CPMP guidelines for injectable formulations (CPMP/ICH/380/95: Maximum shelf-life for sterile products for human use after first opening or following reconstitution).

The formulation of the invention, which has been optimised by keeping the amount and the number of the excipients as low as possible, contains sodium metabisulfite as antioxidant, methyl para-hydroxybenzoate and benzyl alcohol as preservatives and antimicrobials, and sodium edetate as stabilising and chelating agent. The pH which ranges from 3.5 to 3.8 and is preferably 3.7.

After two years of storage at room temperature (25° C), the solution still maintains clear and practically colourless (pale yellow) and the content of the active ingredient is more than 97%; moreover the preservative system still

maintains its microbiological efficacy after 28 days.

Although in the prior art is reported that disodium edetate did not appear to have any further stabilising effect (Lundgren P et al. Acta Pharm Suecica 1970, 7, 133), it has been surprisingly found that in the presence of other ingredients such as preservatives, said chelating agent significantly helps in preventing colouring and in maintaining stable the formulation.

The formula has been adopted in the manufacture, under sterile conditions, of 5 ml vials for parenteral use, to be preferably administered upon subcutaneous infusion by means of a portable mini-pump.

The preparation of the formulation is described in the following example.

EXAMPLE 1

Quantitative composition for pharmaceutical unit.

Compound	Amount (mg)
Apomorphine hydrochloride hemihydrate	50
Sodium metabisulfite	5
Sodium edetate	0.5
Methyl para-hydroxybenzoate	5
Benzyl alcohol	50
1N Hydrochloric acid	q.s. to pH 3.7
Sterile water for injection	q.s. to 5.0 ml

Preparation of the solution.

Sterile water for injection is heated to 80-85°C and methyl para-hydroxybenzoate is therein dissolved. The solution is cooled down to room temperature under mild stirring. Then sodium metabisulfite, sodium edetate, benzyl alcohol are added to the solution, by keeping the preparation under

mild stirring until complete solubilization of all components.

The pH is adjusted with 1N hydrochloric acid to a value ranging from 3.5 to 3.8.

The solution is de-aerated with nitrogen, then apomorphine hydrochloride hemihydrate is added by keeping the preparation under mild stirring till to complete solubilization of the active ingredient.

The resulting solution is diluted to the final volume with sterile water for injection then de-aerated with nitrogen.

For the preparation of the final pharmaceutical formulation, the solution is subjected to filtration sterilisation through a 0.22 μm membrane under nitrogen pressure and subsequently partitioned in 5 ml yellow vials.

EXAMPLE 2

Determination of the stability of the formulation.

Vials containing the formulation were stored under long-term conditions, i.e. at 25±2°C temperature and 60±5 % relative humidity.

Appearance and pH of the solution were monitored at various times. Apomorphine hydrochloride content as well as its degradation products were determined respectively by HPLC and by TLC. The sterility was tested according to F.U. IX Ed., p. 227.

The results are reported in the following table.

Table

Time	Appearance	pH	Apomorphine %	Impur./Degrad. %	Sterility
0 clear yellow	3.09	100.0	<0.3	complies	
3 months	clear yellow	3.05	100.0	0.5	-
6 months	clear yellow	2.99	97.3	1.25	complies
9 months	clear yellow	2.94	98.1	1.25	-
12 months	clear yellow	2.94	97.2	0.9	complies
18 months	clear yellow	2.84	98.6	0.75	-
24 months	clear yellow	3.05	99.8	0.75	complies

The obtained results demonstrate that the formulation of the invention, keeps stable upon storage up to 25°C for two years.

CLAIMS

1. A pharmaceutical formulation in solution for injectable use containing as active ingredient apomorphine hydrochloride hemihydrate in combination with excipients selected from sodium metabisulfite as antioxidant, methyl para-hydroxybenzoate and benzyl alcohol as preservatives and antimicrobials, and sodium edetate as stabilising and chelating agent .

2. A pharmaceutical formulation according to claim 1 wherein apomorphine hydrochloride hemihydrate is in 1% w/v concentration, the antioxidant in 0.1% w/v concentration and the chelating agent in 0.01% w/v concentration.

3. A pharmaceutical formulation according to claims 1 and 2 characterised in that the pH of the solution ranges from 3.5 to 3.8 and is preferably 3.7.

The Patent Office 10

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Claims searched: 1-3 **Date of search:** 29 February 2000

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Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Other: Online: CAS-ONLINE, MEDLINE, WPI, JAPIO, EPODOC

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	CAPLUS abstract accession number 1985:119532 & Boll. Chim. Farm. Mil. vol 123 (9), pages 449-452 (1985). V. Pandolfo *et al.* See abstract.	
A	CAPLUS abstract accession number 1980:591977 & J. Pharm. Sci. vol 69 (8), pages 974-976 (1980). R.E. Wilcox *et al.* See abstract.	
A	CAPLUS abstract accession number 1970:428848 & Acta Pharm. Suecica vol 7 (2), pages 133-148 (1970). P Lundgren *et al.* See abstract.	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.